Kidney and Endocrine

By

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Outline

A. **Effect of CKD on Endocrine system**

1) HPG Axis abnormalities in Uremics
2) CKD and GH
3) Thyroid function in CKD
4) CHO and Insulin metabolism in CKD
5) CKD and PTH (BMD)_____>FGF 23 and Klotho
6) CKD and adrenal gland

B. **Effect of Endocrine system on kidney**

C. **Kidney as an endocrine organ**

Effect of CKD on Endocrine system

- **HPG Axis abnormalities in Uremics**

- At least 50% (some studies say up to 80%) of men :
  - ED
  - ↓ libido
  - ↓ frequency of intercourse
- Improve with dialysis BUT don't normalize
- Even with transplant, ↓ libido and ED remain

- ↓ Gonadal function
  - ↓ testosterone production
- ↓ Hypothalamic-pituitary function
  - Blunted increase in serum LH levels (but total LH increased)
  - ↓ LH secretory burst
  - Var. increase in FSH levels
  - Increased PRL levels

- Impaired spermatogenesis and testicular damage → infertility
- Semen analysis:
  - Decreased volume of ejaculate
  - Low or complete azoospermia
  - Low percentage of motility
- Histologic analysis
  - Decreased spermatogenesis
- Pathologic analysis
  - interstitial fibrosis, calcifications in seminiferous tubules, epididymis, corpora cavernosa, atrophy of sertoli cells

Guvel S, Pourbager M, Torun D, et al. J Androl 2004;25:752-756

- No hypertrophy in sertoli or leydig cells
  - Suggesting hormonal regulation defect of cells as in gonadotropin deficiency or resistance (? functional hypogonadism)
- Etiology of testicular damage in uremia is unclear
  - ??? Plasticizers in dialysis tubing (e.g. phthalate) potentiating the cytotoxic effects ???
  - ….but then why does dialyzing more frequently improve sexual dysfunction…

- Total and free testosterone reduced
- Binding capacity and concentration of sex hormone binding globulin (SHBG) normal
- Stimulation by HCG (LH like action) gives only blunted response in uremic men.
  - Possible factor blocking LH receptor in CKD
  - Reversed by transplantation
- Total plasma estrogen concentration increased

Dunkel L. et al. Kidney Int 1997;51:777-784

- Increased LH in CKD 2/2 :
  - decreased Testosterone release from leydig cells → no feedback inhibition of LH release
  - Decreased metabolic clearance rate of LH with CKD
- NL LH sx in pulsatile fashion
- FSH increased in men with CKD and LH/FSH ratio increased (LH proportionally higher)
- Inhibin made by sertoli cells inhibits FSH
  - Highest FSH in pts with most severe damage to seminiferous tubules
- High FSH poor prognostic sign for spermatogenesis recovery after transplant

- In CKD
  - PRL levels increased but significance unclear as **LH also INCREASED**
- Possible cause of increased PRL levels
  - Hyperparathyroidism
  - Zinc deficiency in CKD

Caticha O et al. J Endocrinol Invest 1996;19:441-448

- Gynecomastia is seen in 30% of HD men
- Pathogenesis unclear
  - ? Elevated PRL levels
  - ? Increased Estrogen : Androgen ratio

Treatment options for men

- Treatment options
  - 6X/week hemo pts show increased testosterone
  - EPO administration shown to improve sexual function
  - Controlling PTH levels to lower PRL
  - Viagra (60-80% response rate)
  - Vacuum device (pump)
  - Testosterone
  - Zinc replacement to raise testosterone levels
  - Transplant

Palmer et al. Adv Ren Replace Ther 2003; 10:48-60

HPG Axis in CKD Women

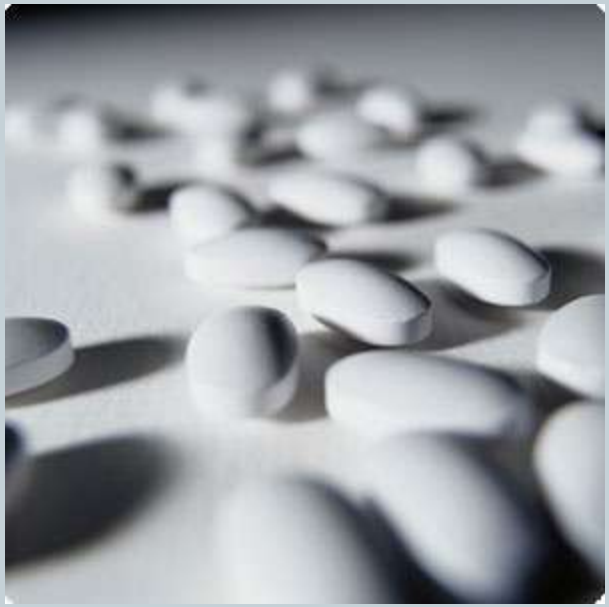
- Major abnormalities:
  - Disturbances in menstruation, anovulation/infertility, decreased libido and reduced ability to reach orgasm
  - Pregnancy occurs rarely BUT fetal wastage markedly increased

- No progesterone effect on endometrium per biopsy
- No preovulatory peak LH and estradiol concentrations
- Increase in circulating endorphin levels in CKD due to reduction in opiod clearance
  - Endorphins inhibit ovulation (possibly by reducing GnRH)

- In CKD, women (like men) have increased PRL levels
  - Hypersecretion autonomous like men
  - Increased PRL levels impair hypothalamus and pituitary function → contribute to sexual dysfunction and galactorrhea

Treatment

- General: Maximize dialysis, correct anemia
- Oligo/Amenorrhea: Administer progestin 5-10 days each month to restore menses
- Restoring fertility in ESRD women discouraged due to complications
  - BUT successful pregnancy in renal transplant
- Decreased libido: No good studies;
  - possible low dose testosterone (but lots of side effects)
  - Bromocriptine (for hyper PRL)
  - Estrogen replacement (if low levels)



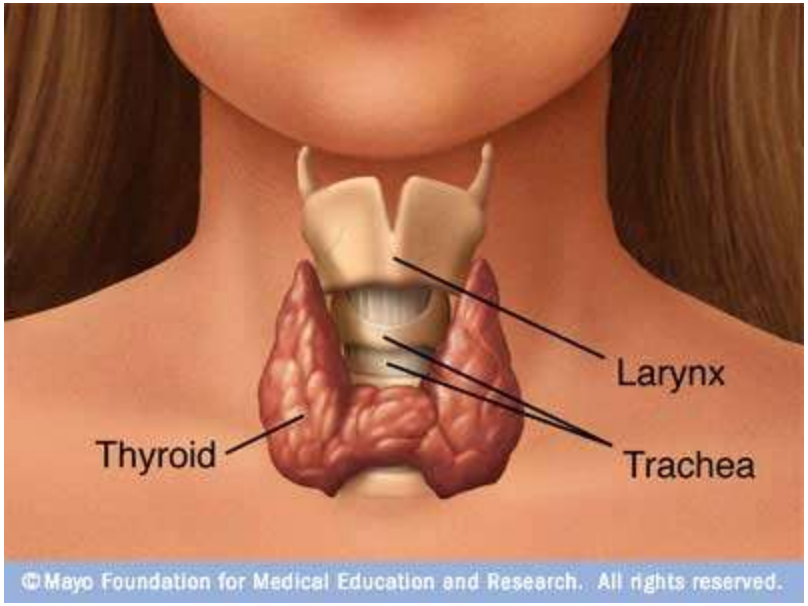
Treatment (cont.)

- Estrogen replacement may improve sexual function in women with low circulating estradiol levels
- Gold standard: renal transplantation

GH in CKD

- Increases in plasma concentration and decreases end-organ responsiveness.
- Levels fall to low-normal values after the institution of dialysis and the administration of EPO
- Growth hormone resistance may be associated with growth retardation in children with CKD. Supraphysiologic doses of rGH can lead to increased growth
- Resistance is due to decreased somatomedin activity, decreased caloric intake, metabolic acidosis. (Uptodate)

Thyroid Function in CKD



Thyroid Function Abnormalities

- ↓ total T3 due to
  - decreased conversion from T4
  - reduced protein binding to thyroid hormone binding globulin and albumin
  - Metabolic Acidosis

Thyroid Function Abnormalities (cont.)

- Normal rT3 (to differentiate from chronic illness where rT3 is enhanced)
- T4 either low or normal
  - Heparin interferes w/ T4 binding to TBG (so transient ↑ after dialysis)
- Normal TSH
  - but blunted and delayed response to TRH

Clinical Manifestations

- Significant overlap in findings between CKD and hypothyroidism:
  - Both have
    - low T3
    - cold intolerance
    - puffy appearance
    - dry skin
    - lethargy
    - fatigability
    - Constipation
  - Slight increase in hypothyroidism in CKD.

Thyroid Structure Abnormalities

- Gland size
  - Increased in CKD
  - Mechanism unclear
- Nodules/Carcinoma
  - Slightly higher frequency of both
  - Mechanism unclear

Carbohydrate Metabolism: Yin and Yang

- Yin
  - Marked fall in insulin clearance leads to improvement in glucose tolerance
  - BUT…
- Yang
  - Glucose control deteriorates with worsening renal function

Insulin Resistance

- Uremia associated with impaired glucose metabolism:
  - Due to impaired tissue sensitivity (especially skeletal muscles)
  - Possible mechanism:
    - Increased hepatic gluconeogenesis
    - Reduced hepatic/skeletal muscle uptake
    - Impaired intracellular metabolism due to decreased glycogen synthesis, or decreased oxidation to CO_2
    - accumulation of nitrogenous wastes, reduced excretion of adiponectin, inflammatory cytokines and hyperparathyroidism
- NOTE: Interestingly, actions of insulin such as K+ uptake, proteolysis inhibition, maintained in renal failure

Insulin Resistance Treatment

- Both HD and PD improve insulin resistance consistent with role of uremic toxins
- PD restores higher insulin sensitivity than HD
- Correction of anemia with EPO markedly increases (~50% in one study) insulin-induced glucose utilization
- ACEI improve insulin resistance, hyperinsulinemia, glucose intolerance in CKD
- METFORMIN and TZDs are CI

Insulin Resistance Treatment

- Calcitriol therapy:
  - Enhances insulin release and improves glucose tolerance.
  - Its effects independent of PTH
- PTH
  - Excess PTH may interfere with pancreatic B-Cells ability to secrete insulin
    - Possible mechanism: PTH causes increased intracellular calcium which decreases cell ATP concentration and Na-K ATPase activity

Insulin Clearance

- Decline in insulin clearance seen when GFR < 15-20cc/min
- NOTE: at this GFR also see concomitant decline in hepatic insulin metabolism
- This defect reversed with adequate dialysis

Adrenal Gland

- A study of patients on maintenance hemodialysis found that an elevated predialysis serum cortisol concentration was predictive of increased morbidity, as defined by the need for hospitalization [uptodate]

Cont.,

- There is reduced PPB and increased clearance of dexamethasone .
- There is reduced PPB but decreased clearance of prednisolone . The fall in clearance may explain the apparently higher incidence of steroid-induced side effects when prednisolone is used in renal failure.
- The pharmacokinetics of methylprednisolone are unaltered.

Effect of Endocrine system on kidney

SCIENCE IN RENAL MEDICINE www.jasn.org

The Renal Manifestations of Thyroid Disease

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J Am Soc Nephrol **23:** 22–26, 2012

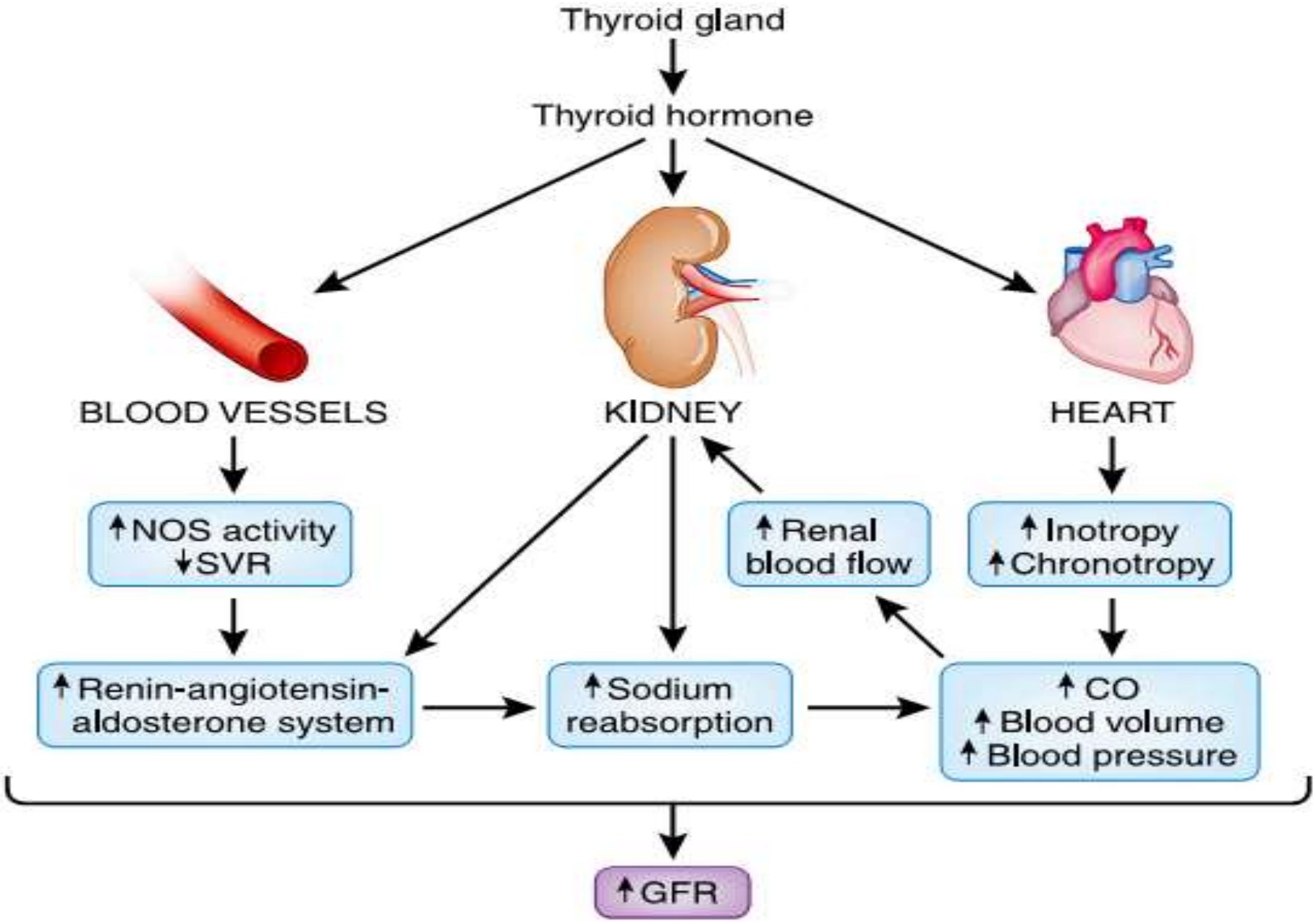
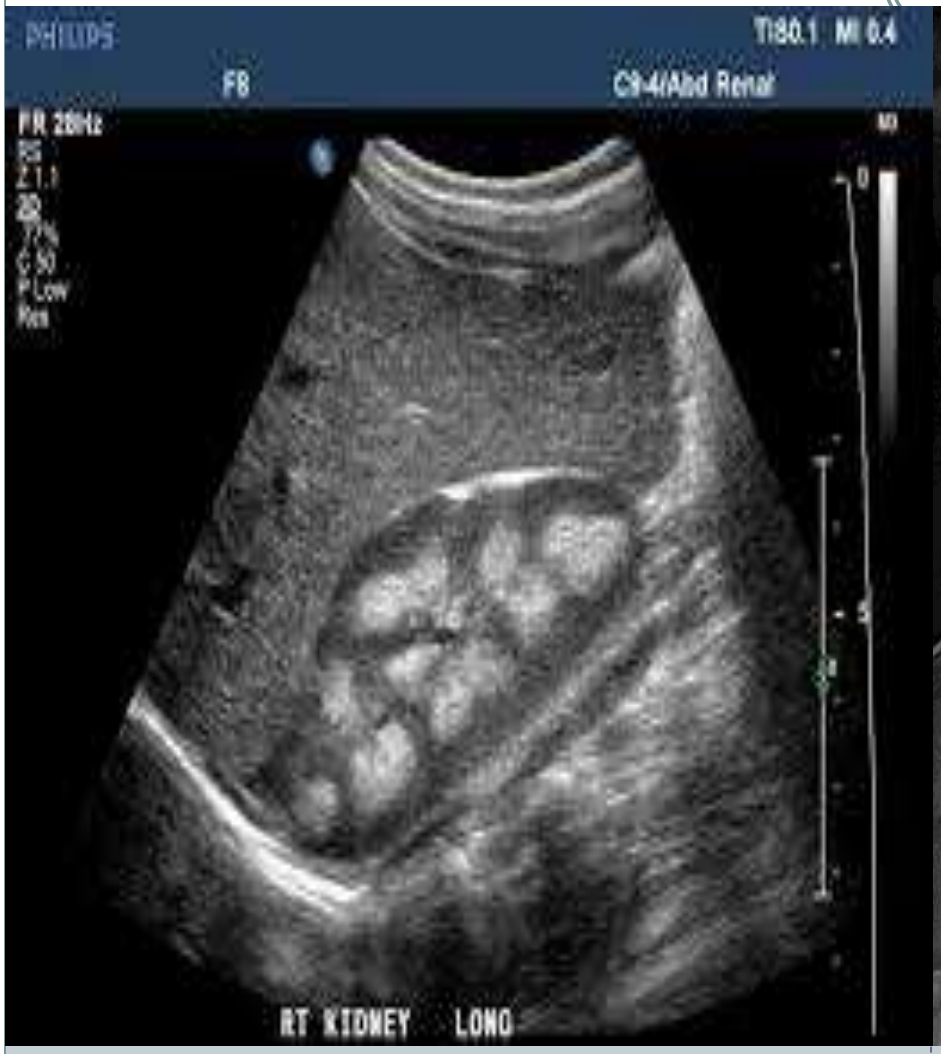
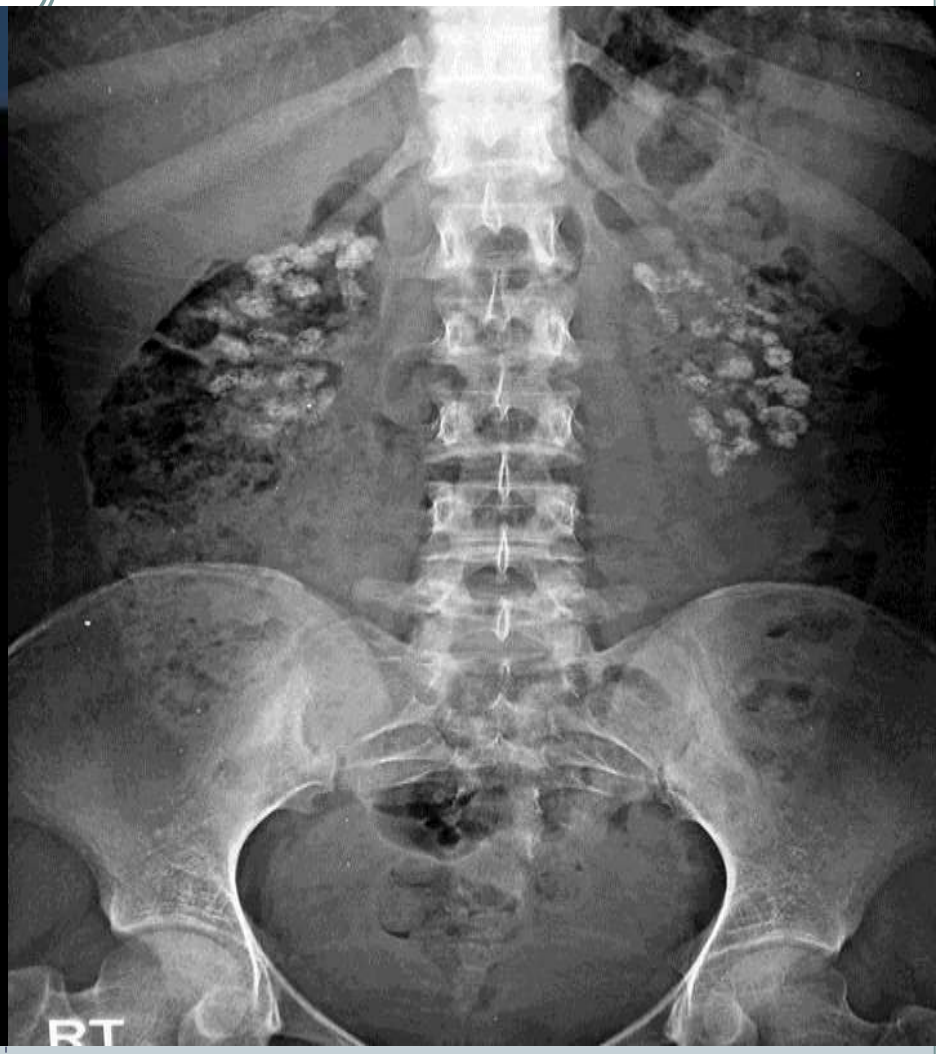


Figure 1. Multiple direct and indirect effects of thyroid hormone on GFR. NOS, nitric oxide synthase; SVR, systemic vascular resistance; CO, cardiac output.

1ry HPT





Acromegaly

European Journal of Endocrinology (2010) **162** 1035–1042 ISSN 0804-4643

CLINICAL STUDY

The kidney in acromegaly: renal structure and function in patients with acromegaly during active disease and 1 year after disease remission

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Cont.,

- **In conclusion**

1. Acromegaly is responsible for structural abnormalities and renal function impairment because it induces an increase in renal size together with an increase in CrC, decrease in Na& K FEs, hypercalciuria, hyperphosphaturia, increase in mA levels.

2. These alterations seem to revert only partially after the correction of GH and IGF1 excess by treatment.

Renal endocrinology: The new frontier

- Hormones: RAS, EPO, vit D3.
- Enzymes: kallikreins, which produce hormones in other, distant sites.
- Local hormones: PGs, Ets and adrenomedullin.
- Target organ for: aldosterone, angiotensin, and the natriuretic peptides.

Indian J Endocrinol Metab. 2012 Mar-Apr; 16(2): 154–155.

على قدر الهدف يكون الانطلاق

ففي

" طلب الرزق قال:" فامشوا

" وللصلاة قال:" فاسعوا

" وللجنة قال:" وسارعوا

"وأما إليه فقال:"ففروا إلى الله

THANK YOU